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Drug Reactions in HIV/AIDS

Adverse reactions to drugs are frequent in patients with human immunodeficiency virus (HIV) infection and AIDS. The most commonly prescribed drug for AIDS patients is trimethoprim-sulfamethoxazole (TMP-SMX); it is also the most common source of adverse reactions. Up to 40% of patients receiving high-dose TMP-SMX develop a maculopapular diffuse rash, often with fever and malaise. Similar reactions have been reported with clindamycin, diapsone, pyrimethamine/sulfadoxine, aminopenicillins, clavulanate, thalidomide, atovaquone, nevirapine, delavirdine, rifampin, probenecid, and 1592 (a new antiviral drug).

The cause of these reactions is not clear. Immunologic processes might be involved, since patients with HIV and AIDS demonstrate immunoactivation as well as immunodeficiency. A polyclonal increase of immunoglobulins (including IgE), increased circulating immune complexes, and an increased number of activated $CD8^+$ cells may be secondary to various infections. Abnormal hepatic metabolism may result in the persistence of drug metabolites that act as antigens or have direct cellular toxicity. Alternatively, an incompetent immune system may fail to clear the metabolites. Finally, incidence of certain viral infections, such as herpes simplex virus, hepatitis B virus, cytomegalovirus, and Epstein-Barr virus (EBV), is increased in patients with HIV and AIDS. These infections may stimulate the immune system, predisposing the patients to drug reactions such as that between EBV and aminopenicillins. There is no conclusive evidence that the incidence of IgE-mediated reactions to drugs, such as penicillin-induced anaphylaxis, is increased in patients with HIV/AIDS. Rather, the incidence of some adverse drug reactions seems to increase with advancing immunodeficiency. A possible participation of hepatic drug metabolism may explain the success of incremental dosing (as with nevirapine and delavirdine) and desensitization protocols in minimizing the problems.

The most common clinical presentation of an adverse drug reaction in patients with HIV/AIDS is rash. The rash, which starts 7 to 12 days after initial exposure to the culprit agent, is usually diffuse, erythematous, maculopapular, and pruritic and is frequently accompanied by fever and malaise. Conjunctivitis is common, but mucous membrane involvement is not. Susceptible patients may have identical or nearly identical symptoms from several agents. More severe reactions, such as Stevens-Johnson syndrome, bullous lesions, and toxic epidermal necrolysis, also may occur. Hepatic and hematologic abnormalities can stem from immune-mediated injury or direct toxicity; rare cases have been reported of eosinophilic pneumonia possibly secondary to drugs.

The diagnosis of adverse drug reactions rests mainly on a good history, especially a detailed drug history, timing of introduction of the suspected agent, and clinical symptoms and physical examination.

Withdrawal of the offending agent is usually successful in treating the reactions. Although severe bullous rashes are often treated with corticosteroids, the effects of this treatment are difficult to assess. We have noted remarkable responses to intravenous immunoglobulin infusion in a few seriously ill patients with bullous skin rashes.

Although avoiding the offending agent is the safest method to treat the problem, it may not be the best approach if the agent is the drug of choice and there is no tolerated alternative. In such circumstances, a careful desensitization may be attempted. Desensitization has been successful with TMP/SMX, clindamycin, sulfadiazine, and other agents, but probably should not be attempted for such serious or life-threatening reactions as anaphylaxis, bullous dermatitis, or renal or hepatic failure.

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Latex Allergy—The Latest Insights

Urticaria to latex has been reported as early as 1927 and more recently in 1979. Fatal reactions to latex-tipped barium enema catheters brought attention to the potentially serious nature of the allergy around 1990. In recent years, awareness of the condition has risen, as has exposure to latex: more than 40,000 products contain latex, and latex gloves are omnipresent in health care settings. As a result, more and more latex-sensitive patients are being identified. Groups reported to have high prevalence rates of latex allergy include health care workers, dental workers, rubber industry workers, housekeepers, spina bifida patients, and patients undergoing frequent catheterizations or multiple surgeries.

Two potential mechanisms for sensitization are common: direct contact and inhalation of aerosol latex proteins carried on the cornstarch of powdered gloves. Latex-sensitive individuals experience symptoms that vary from localized hand symptoms such as itching or urticaria to a wide range of systemic reactions including

generalized urticaria, sneezing, tearing, coughing, wheezing, and even anaphylaxis with hypotension shortly after exposure to latex products. Some investigators have noted a progression of symptoms in health care workers from contact dermatitis to localized urticaria to systemic IgE-related symptoms. On the other hand, a significant number of patients who develop systemic IgE symptoms do so without any preexisting contact dermatitis.

In a patient known to have other allergies, it can be difficult to determine whether latex exposure is precipitating symptoms or simply aggravating them. In questionnaires, many people self-report symptoms that could be from latex exposure, but few cases are confirmed by diagnostic tests. Recent epidemiologic studies have reported prevalence rates in health care workers ranging from 2.9 to 17%, but ascertainment bias may be a factor in those results. Better-designed epidemiologic studies as well as longitudinal studies must be undertaken.

The immunologic mechanism for systemic reactions to latex is a type I hypersensitivity mediated by IgE antibodies directed against latex rubber proteins. According to one study, 57 of the 200 proteins in latex bind to human IgE. Seven sensitizing latex proteins have been identified, cloned or partially characterized, and assigned allergen designations of Hev b1–b7 by the International Union of Immunological Societies. A high percentage of patients who are latex sensitive are also positive for at least one food skin test, suggesting epitopes common to both latex and food allergens. Foods that cause allergic reactions in latex-sensitive patients include banana, avocado, kiwi, chestnut, potato, cherry, apricot, papaya, passion fruit, and melon.

Three FDA-approved latex-specific IgE in vitro tests are available: Alastat, CAP, and Hycor. Although these assays claim high sensitivity and specificity, their accuracy and reliability can only be determined with broader clinical experience in various populations. A challenge procedure may be used to clarify the diagnosis in patients who have clinical histories that conflict with skin test or in vitro test results, and developing standardized challenge procedures is an important area of research. There is no standardized skin test reagent—testing patients with extracts of unknown potency has resulted in systemic reactions, limiting the use of skin testing. A multicenter clinical trial using a Food and Drug Administration–approved non-ammoniated latex extract is underway.

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Antileukotrienes—1997 and Beyond

Antileukotrienes represent a new class of asthma medication. They modulate inflammation, they have a mild bronchodilator activity, and their virtual lack of side effects represents an advantage over many other antiasthmatic compounds. Antileukotrienes have the ability to counter most of the basic pathogenic mechanisms of asthma, and they modify increased vascular permeability and edema formation, increased mucus production, bronchoconstriction, and cellular inflammatory exudate.

Two main classes of agents modulate leukotrienes, the leukotriene receptor antagonists and the inhibitors of key enzymes involved in the synthesis of leukotrienes. The latter class can be divided into two further groups: those that inhibit 5-lipoxygenase [5-LO] and those that inhibit the activity of 5-lipoxygenase activating protein (FLAP). Of the many compounds currently under study, only two agents, zafirlukast and zileuton, have received approval from the Food and Drug Administration (FDA).

The potential usefulness of the antileukotrienes has been demonstrated in various experimental and clinical studies. Their mechanisms vary, suggesting that agents within the leukotriene category should be substituted if clinical response is not adequate. For example, virtually all the receptor agonists improve dose response, and some agents, such as zafirlukast and the FLAP inhibitor BAY 10005, block both early- and late-phase allergen challenges.

Many agents block hyperresponsiveness as measured by methacholine or histamine inhalation challenge. They include the receptor antagonists zafirlukast and pranlukast and the synthesis inhibitors BAY 10005 and MK-886. Almost all of the leukotriene antagonists and inhibitors have been shown to block exercise-induced asthma and cold air challenge to some degree.

It is thought that antileukotrienes might be particularly effective in the subgroup of patients with aspirin idiosyncrasy. The leukotriene antagonist SKF-104353 was shown to be an effective blocker in five subjects studied; similarly, pranlukast in a single dose of 225 mg showed an impressive effect in six aspirin-sensitive patients. A single dose of 750 mg of montelukast blocked an inhaled lysine aspirin challenge in patients with aspirin sensitivity, and zileuton in a dose of 600 mg four times a day for 6 to 8 days also was found to attenuate aspirin challenges and decrease urinary LTE_4 levels. In the latter study, the agent was also found to attenuate nasal, gastrointestinal, and dermal responses to aspirin.

Many researchers have studied antileukotrienes in clinical asthma. For example, compared with baseline measurements, patients receiving 40 mg of zafirlukast experienced a 46% decrease in nighttime awakening, a 30% decrease in albuterol use, and a 26% improvement in daytime symptoms. The oral compound MK-571 has also been found to improve asthma symptoms and pulmonary function and decrease beta-agonist use. Verlukast has shown similar effects, as have montelukast, pranlukast, and zileuton.